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Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk

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Running Head: The SUMMIT trial

Trial Registration: NCT01313676 (113782): Study to Understand Mortality and Morbidity In COPD Trial (SUMMIT)

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Abstract (295 words)

Background. Chronic obstructive pulmonary disease (COPD) often coexists with cardiovascular disease. Treatments for airflow limitation may improve survival and both respiratory and cardiovascular outcomes.

Methods. In a double-blind randomised controlled trial, 16,485 patients with symptomatic moderate COPD and heightened cardiovascular risk received once daily inhaled placebo, fluticasone furoate (100 µg), vilanterol (25 µg) or the combination. Primary outcome was all-cause mortality, and secondary outcomes were on-treatment rate of decline in forced expiratory volume in one second (FEV_1) and composite of cardiovascular events.

Findings. Compared with placebo, all-cause mortality was unaffected by combination therapy (hazard ratio (HR) 0·878, [95% confidence interval 0·739 to 1·042]; 12·2% relative reduction; P=0·137) or the components (fluticasone furoate, HR 0·911 [0·767 to 1·081]; vilanterol, HR 0·962 [0·813 to 1·139]), and therefore secondary outcomes should be interpreted with caution. Rate of decline in FEV_1 was reduced by combination therapy (38 *versus* 46 mL/year for placebo, difference 8 mL/year [1 to 15]) with similar findings for fluticasone furoate (difference 8 mL/year [1 to 14]) but not vilanterol (difference -2 mL/year [-8 to 5]). Combination therapy had no effect on composite cardiovascular events (HR 0·926 [0·750 to 1·143]) with similar findings for fluticasone furoate (HR 0·896 [0·723 to 1·111]) and vilanterol (HR 0·988 [0·802 to 1·217]). All treatments reduced the rate of moderate and severe exacerbations. There were no reported excess risks of pneumonia or adverse cardiac events in the treatment groups.

Interpretation. In patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes, reduced exacerbations and was well tolerated. Fluticasone furoate, alone or in combination with vilanterol, appeared to reduce FEV_1 decline.

Funding. The study was funded by GlaxoSmithKline.

Keywords: COPD; cardiovascular disease; mortality; survival; fluticasone furoate; vilanterol; combination therapy, rate of decline of FEV_1.

Research in context

Evidence before this study

Up to November 2015, we searched PubMed and ClinicalTrials.gov for published or on going studies that examined the treatment of patients with concomitant chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) with inhaled corticosteroids or long-acting beta-agonists with the following search terms: “COPD”, “cardiovascular disease”, “inhaled corticosteroids”, “long-acting beta-agonists”. The search also used our familiarity with the medical literature and research in progress within the specialty. There were no adequately powered trials, and only a limited number of post-hoc or subgroup analyses of larger trials, to provide clinicians with evidence to make decisions about the treatment of patients with concomitant COPD and CVD.

Added value of this study

Our findings bridge a crucial gap by providing clinicians with evidence regarding inhaled treatments for patients with concomitant moderate COPD and CVD. In this patient group, combined inhaled corticosteroid and long-acting beta-agonist treatment had no effect on overall mortality or cardiovascular events. In contrast to inhaled beta-agonist therapy, inhaled corticosteroid treatment was associated with a reduction in the rate of decline of lung function. All treatments reduced the rate of moderate and severe exacerbations.

Implications of all of the available evidence

Treatment with a combination of an inhaled corticosteroid and long-acting beta-agonist has documented benefits in COPD. In patients with moderate COPD and CVD, these benefits do not extend to reductions in overall mortality or cardiovascular events. However, inhaled corticosteroid therapy does appear to inhibit the rate of decline in lung function.

Introduction

Chronic obstructive pulmonary disease (COPD) often coexists with other chronic diseases that can contribute to patients' health status and prognosis (1-3). Impaired pulmonary function is particularly associated with cardiovascular morbidity and mortality, and patients with COPD are at greater risk of cardiovascular disease compared with age and sex-matched individuals without COPD (4-7). Furthermore, more patients with moderate airflow limitation die from cardiovascular disease and lung cancer than from the respiratory consequences of COPD (8, 9). Several mechanisms have been proposed to link COPD with the increased risk of cardiovascular disease including shared risk factors (e.g., smoking), systemic inflammation (10), vascular dysfunction (11) and sedentary activity secondary to the functional consequences of COPD (12). Conversely, treatments that improve lung function and reduce exacerbations would be anticipated to reduce these factors thereby improving both respiratory and cardiovascular outcomes (13).

The current Global Initiative for Chronic Obstructive Lung Diseases (GOLD) strategy document has highlighted the need to assess and treat comorbidities in COPD (1). However, the evidence base is incomplete and most advice comes from expert statements or from secondary analyses of large studies. Indeed, there is disagreement on the potential effects of COPD treatment on cardiovascular outcomes. Some evidence suggests that in patients with COPD, inhaled beta-agonist therapy may be associated with adverse cardiovascular outcomes (14). On the other hand, in secondary analyses of the TOwards a Revolution in COPD Health (TORCH) trial (15), there were apparent reductions in respiratory and cardiovascular mortality with inhaled salmeterol and fluticasone propionate. This was the rationale for the current trial where we address the hypothesis that inhaled corticosteroid and long-acting beta-agonist therapy could improve mortality in patients with both COPD and cardiovascular disease.

In the Study to Understand Mortality and MorbidITy (SUMMIT), we prospectively assessed whether inhaled treatment with the corticosteroid, fluticasone furoate, and the long-acting beta-agonist, vilanterol, would improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk.

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Methods

Details of the study design and the analysis approach were published previously (13).

Patients

Between 24th January 2011 and 12th March 2014, we recruited patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were 40 to 80 years old, diagnosed with COPD and had a post-bronchodilator forced expiratory volume in one second (FEV_1) ≥50 and ≤70% of the predicted value (16), ratio of post-bronchodilator FEV_1 to forced vital capacity (FVC) ≤0·70, and ≥2 on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Cardiovascular disease was defined as coronary artery disease, peripheral arterial disease, stroke, myocardial infarction or diabetes mellitus with target organ disease. Increased cardiovascular risk was defined as ≥60 years and receiving medication for ≥2 of the following: hypercholesterolaemia, hypertension, diabetes mellitus or peripheral arterial disease. Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery, receiving long-term oxygen or oral corticosteroid therapy, severe heart failure (New York Heart Association Class IV or ejection fraction <30%), life expectancy <3 years, and end-stage chronic renal disease (13). All patients provided written informed consent. The study was approved by local ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study is registered on clinicaltrials.gov as NCT01313676.

Study Design

This was a prospective double blind parallel group placebo controlled event-driven randomised trial conducted at 1,368 centres in 43 countries. Participants were allocated equally to one of four treatments (placebo, fluticasone furoate (100 µg; GlaxoSmithKline), vilanterol (25 µg; GlaxoSmithKline) or the combination of fluticasone furoate and vilanterol (100/25 µg; Relvar®/Breo®, GlaxoSmithKline)) administered once daily as a dry powder with the use of an inhaler (Ellipta®, GlaxoSmithKline).

The use of all inhaled corticosteroids and inhaled long-acting bronchodilators was discontinued at least 48 hours before study entry, although other COPD medications such as theophyllines were permitted (13). Patients unable to tolerate withdrawal of therapy were excluded from study entry. After randomisation, patients were seen every 3 months to confirm vital status and record adverse events. Post-bronchodilator spirometry was performed every 3 months and health status was assessed at 3 months then every 6 months. An independent data monitoring committee (IDMC) performed safety reviews every 6 months, and one pre-defined interim efficacy analysis was performed after a total of approximately 500 deaths had occurred. The stopping guideline for efficacy was the Haybittle-Peto method (one-sided P value of 0·00005) in order to have a negligible impact on the final significance level.

Randomisation and masking

Participants were randomly assigned through a centralised randomisation service in permuted blocks. The randomisation schedule was generated using the GSK validated randomisation software RANDALL. A separate randomisation schedule was produced for each country.

Treatment was double blind (masking was achieved with Ellipta® inhalers of identical appearance) with only the database administrators having knowledge of treatment assignment.

Outcome Measurements

The primary efficacy outcome was the time to death from any cause, regardless of maintenance of study medication. Categorisation of cause of death was performed by a clinical end-point committee using all available information including study data, death certificates, autopsy findings, and health records (17). Secondary end-points were on-treatment rates of decline in FEV_1 and the on-treatment composite cardiovascular end-point of cardiovascular death, myocardial infarction, stroke, unstable angina and transient ischaemic attack. Exacerbations were an additional outcome. Moderate exacerbations were defined as a symptomatic deterioration requiring treatment with antibiotic agents and/or systemic corticosteroids, whereas severe exacerbations were defined as events leading to hospital admission.

Safety Evaluation

Adverse events and medications were reviewed at each study visit. All terms that could relate to a specific adverse event were compiled to provide a more comprehensive assessment of a specific safety term. The IDMC oversaw the ethical and safety interests of the patients by periodically reviewing cumulative data on serious adverse events in addition to the interim analysis.

Statistical Analysis

This was an event-driven study where follow up continued until at least 1,000 deaths had occurred. All data analysis decisions were determined prior to unblinding. To ensure no bias in the ascertainment of survival status, a "common end date" was determined several months in advance. This common end date was selected so that there would be at least 1,000 deaths by this date. The common end-date was set at 25 January 2015, and sites were required to ascertain the survival status of their patients on or after this date.

We assumed an annual placebo event rate of 3.0% per year (13, 15) and the study was designed to have 90% power to detect a 30% reduction in all-cause mortality (hazard ratio=0·70) on combination therapy compared with placebo at the two-sided 1% significance level (13). Statistical significance was taken as two-sided $P<0{\cdot}05$. To control for multiplicity of testing of combination treatment versus placebo across endpoints, a closed testing procedure ("gatekeeper") approach was planned. The hierarchy was the primary endpoint followed by the rate of decline in FEV_1 followed by the composite cardiovascular endpoint. If significance at the 5% level was not achieved for the primary endpoint for the comparison of combination treatment with placebo, then the tests for the secondary and other efficacy endpoints would be interpreted as descriptive only. The primary efficacy endpoint was analysed using a Cox proportional hazards regression model allowing for covariates of age and sex. A similar model was used for the time to the first on-treatment composite cardiovascular event, with the inclusion of two additional covariates: the presence of ischemic heart disease (e.g. previous MI) or vascular disease (e.g. previous stroke) at baseline. The rate of decline was analysed using a random coefficients model allowing for covariates of age, sex and baseline FEV_1. The slope was calculated from 90 days, to ensure that any initial short term increase in FEV_1 did not overestimate any treatment benefit on the slope. The frequency of exacerbations was analysed with the use of a generalized linear model (assuming a negative binomial distribution, which accounts for variability among patients in the number and frequency of exacerbations), with the number of exacerbations as the outcome and the logarithm of time during which treatment was received as an offset variable. Adverse events of special interest were compared between treatment groups using Kaplan-Meier estimates.

Scientific oversight of the trial was provided by a scientific steering committee composed of six academic researchers and three employees from GlaxoSmithKline, who were collectively responsible for the study design and conduct, for approval of the statistical analysis plan, and for the review and interpretation of the data.

Role of the funding source

The study was designed by the sponsor in collaboration with the academic members of the steering committee. The sponsor was responsible for the running of the trial, data collection, and statistical analysis. Statistical analyses were performed by a contract research organisation on behalf of, and with oversight from, employees of the sponsor. The first draft of the manuscript was written by the primary academic author, and all the authors worked collaboratively to prepare the final content. All authors made the decision to submit the manuscript for publication. All the authors had full access to the data and vouch for the accuracy and completeness of all data and analyses, and for the fidelity of the study to the protocol. The corresponding author had access to all the data and had final responsibility for the decision to submit for publication.

Results

Study Population

Of 23,835 patients screened, 16,590 underwent randomisation (Figure 1). Of these, 22 subjects never took study medication and the safety population therefore consists of 16,568 patients. Data from 5 centres (83 patients) were excluded from the efficacy analysis because of failure to meet the standards of Good Clinical Practice and ethical practice, and were closed before the study ended. Thus, a total of 16,485 patients were included in the intent-to-treat efficacy (ITT) population (Table 1).

Approximately one-third of patients stopped inhaled corticosteroids prior to study entry, with a similar proportion stopping long-acting beta-agonists. Thirty nine percent of patients reported having had a COPD exacerbation in the year before entry. A subset of 27% of patients who completed questionnaires were symptomatic with mean baseline scores of 45-46 across all treatment groups on the St. George's Respiratory Questionnaire (SGRQ) scale, and 18-19 on the COPD Assessment Test (CAT). Three-quarters of patients had established cardiovascular disease or diabetes mellitus with end-organ disease (n=11,662, 71%), while a quarter (n=4,641, 28%) had an increased risk of cardiovascular disease only. Blood pressure at entry was on average ~135/80 mmHg across all treatment groups. There were 182 patients who failed to meet the cardiovascular entry criteria but were included in all analyses. More patients withdrew from study medication in the placebo group (29%) than in the three other groups: the lowest withdrawal rates were seen with combination therapy (23%). The maximum follow-up was 4 years; median study exposure was 1·8 years and was similar across all treatment arms, with an interquartile range of 1·2 to 2·6 years. Treatment exposure was highest with combination therapy followed by vilanterol, fluticasone furoate and then placebo (Table 2). The rate of adherence to treatment was similar in all groups with only 494 patients (3%) taking <80% of prescribed study medication doses.

Mortality

Vital status was known for 16,480 (99·97%) of the 16,485 patients in the ITT population. At the common end date there were 1,037 deaths: 24 deaths occurred after the common end date with 10 still receiving study medication. The proportions of deaths from any cause were 6·7% in the placebo group, 6·1% in the fluticasone furoate group, 6·4% in the vilanterol group, and 6·0% in the combination therapy group. Compared with placebo, the absolute risk reduction for death with combination therapy was 0·7%: a hazard ratio of 0·878 (95% confidence interval [CI], 0·739 to 1·042; P=0·137) corresponding to a relative reduction of 12·2% (95% CI, -4·2 to 26·1%; Figure 2). There was no significant heterogeneity according to age, sex, baseline therapy or presence of cardiovascular disease. The risk of death in the fluticasone furoate group and the vilanterol group did not differ from the placebo group (Table 3). Overall, 43% of deaths were adjudicated as due to cardiovascular causes, 23% to cancer, and 13% to pulmonary causes (Table 3).

Secondary outcomes

On-treatment rates of FEV_1 decline were 46 mL per year in the placebo group, 38 mL per year in the fluticasone furoate group (difference from placebo 8 mL per year, 95% confidence interval, 1 to 14 mL per year), 47 mL per year in the vilanterol group (difference from placebo -2 mL per year, -8 to 5 mL per year) and 38 mL per year in the combination treatment group (difference from placebo 8 mL per year, 1 to 15 mL per year) (Figure 3 and

Table 3). As combination treatment did not reduce overall mortality (the primary outcome) statistical inferences from these findings cannot be made.

The proportions of patients with an on-treatment composite cardiovascular end-point were 4·2% in the placebo group, 3·9% in the fluticasone furoate group, 4·4% in the vilanterol group and 4·2% in the combination therapy group (Table 3). Compared with placebo, combination therapy had no effect on the composite cardiovascular endpoint (HR 0·926, 95% confidence interval 0·750 to 1·143). Similarly, the composite cardiovascular end-point in the fluticasone furoate (HR 0·896, 0·723 to 1·111) and vilanterol (HR 0·988, 0·802 to 1·217) groups did not differ from placebo.

Exacerbations

Compared with placebo, the percent reduction in moderate and severe exacerbations was 12% (95% confidence interval 4%-19%) for the fluticasone furoate group, 10% (2%-18%) for the vilanterol group, and 29% (22%-35%) for the combination group (Table 3). For exacerbations requiring hospital admissions the percent reduction was 18% (3%-31%) for the fluticasone furoate group, 20% (5%-32%) for the vilanterol group, and 27% (13%-39%) for the combination group, compared with placebo. As with FEV_1 decline, these findings can only be viewed descriptively as combination treatment did not reduce overall mortality (the primary outcome).

Safety

Adverse events were reported by 68% of the patients in the study, and serious adverse events were reported by 23% of the patients. The most frequently reported adverse event was an exacerbation of COPD. There was no excess of pneumonia, cardiac disorders or arrhythmias across all treatment groups. There were no differences in the incidence of fractures or eye disorders whereas more patients allocated to fluticasone furoate experienced local steroid effects (oral candidiasis and hoarseness) (Table 2).

Discussion

SUMMIT is the largest survival study to date of an inhaled corticosteroid and long-acting beta-agonist in patients with COPD and heightened cardiovascular risk. In over 16,000 patients, treatment with inhaled fluticasone furoate and vilanterol had no significant effect on all-cause mortality or cardiovascular outcomes. Inhaled therapy improved lung function and fluticasone furoate, alone or in combination with vilanterol, was associated with a reduction in the rate of decline in FEV_1. We conclude that inhaled combination fluticasone furoate and vilanterol does not affect overall survival or cardiovascular outcomes.

In the previous TORCH trial (9), inhaled combination therapy with salmeterol and fluticasone propionate appeared to be associated with a 2·6% absolute reduction (17·5% relative risk reduction) in all-cause mortality in patients with moderate-to-severe COPD although this fell short of statistical significance (P=0·052). Many of these deaths were cardiovascular and a *post hoc* analysis suggested that the combination treatment might reduce cardiovascular mortality (15). In SUMMIT, we tested the hypothesis that greater mortality reductions might occur in populations with COPD that are enriched for cardiovascular disease. We report that the point estimate for all-cause mortality was 0·7% (12·2% relative reduction) lower with combined fluticasone furoate and vilanterol therapy than with placebo. This difference was not statistically significant and the trial did not reach its primary end-point. However, it should be acknowledged that a clinically meaningful difference in mortality has not been entirely excluded since the 95% confidence interval for the hazard ratio encompasses a 26% reduction in the risk of dying.

The absence of an effect on overall survival has a number of potential explanations including a failure to take sufficient active therapy, inadequate dosing, or a lack of effect on lung function in patients with less severe COPD. However, recorded adherence to treatment was high and patients receiving fluticasone furoate experienced expected side effects. As anticipated, we observed improvements in FEV_1 with both fluticasone furoate and vilanterol confirming the efficacy of the two interventions. We therefore do not believe that the failure to reach the primary endpoint was due to inadequate dosing or a lack of an effect on COPD. Finally, it is interesting to speculate whether more prolonged follow up would have been beneficial to increase the number of events, to extend drug exposure, and to acquire a more precise point estimate of a potential treatment effect.

We pre-specified the first secondary endpoint as the rate of decline in FEV_1 to assess the efficacy of the trial intervention on respiratory pathophysiology and disease progression. Given the hierarchical analysis plan, these findings should not be viewed as conclusive since the primary endpoint was not met. Intriguingly, we did observe that the components appeared to have a differential treatment effect on the rate of decline in FEV_1. There was a consistent reduction in the rate of decline in FEV_1 associated with fluticasone furoate-containing arms that was not observed with vilanterol. When evaluating the impact of a decrease of 8 mL per year, it should be taken into account that in the general population FEV_1 normally declines at a rate of 25-30 mL per year and that this mean reduction could be viewed as between a third and half of the excess decline observed in this study population. In addition, up to half of patients with COPD do not experience an accelerated decline suggesting that some patients may experience larger effects (18). This observation suggests that medications that include inhaled corticosteroids may inhibit lung inflammation and the decline in lung function attributable to COPD as noted in much smaller studies of patients with moderate COPD (19). This also suggests that treatment of COPD at an earlier stage of the disease process has the potential for long-term benefits in preservation of lung function. The beneficial effect of inhaled corticosteroids on FEV_1 decline in this study as well as in the TORCH study (20) likely reflects the large sample size and power of these studies compared with earlier trials (21-24). It is plausible that inhaled corticosteroids could affect decline in lung function without having a notable effect on overall mortality given that we only followed study participants for slightly less than 2 years, a follow-up period too short to capture a mortality benefit in those with only moderate disease. There were fewer moderate and severe exacerbations in all treatment arms in SUMMIT supporting a beneficial effect for COPD drug treatment, even in patients with milder COPD.

For many clinicians and especially cardiologists, there has been concern about the use of inhaled beta-agonists in patients with cardiovascular disease. Some have suggested that inhaled beta-agonists are pro-arrhythmic and may precipitate myocardial infarction or sudden death (14). In our study, we have intentionally enriched our study population with patients who had established, or were at high risk of, cardiovascular disease. Despite this enrichment, we detected no evidence of adverse cardiovascular events either self-reported or as adjudicated cardiovascular endpoints. The point estimates for all trial interventions were favourable and there was no suggestion of an adverse cardiovascular safety signal. We believe that the current study highlights the cardiovascular safety of using long-acting beta-agonists and inhaled corticosteroids in patients with COPD and heightened cardiovascular risk. Despite the enrichment for patients with cardiovascular risk, we observed lower rates of cardiovascular events than anticipated. This may reflect the high use of highly effective preventative treatments, such as antiplatelet, lipid-lowering and renin-angiotensin system inhibitor therapies, in our study population. These evidenced-based therapies will substantially reduce cardiovascular events and this may have hindered our ability to demonstrate a beneficial effect with the study intervention.

An increased risk of pneumonia was one of the main findings of the TORCH trial (9, 25) and has been found in other studies of inhaled corticosteroids in patients with COPD (26), including fluticasone furoate (27). Reassuringly, we observed no such effect in our study. Indeed, there were no detectable differences in pneumonia rates between patients receiving placebo and those receiving fluticasone furoate alone or in combination with vilanterol. This likely reflects the lower rates of pneumonia and the lower rates of bacterial colonisation in the airways of patients with milder COPD (28). The apparent lower risk of pneumonia in patients receiving vilanterol alone was unanticipated and we do not have a ready explanation for this unexpected finding.

In conclusion, in patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol does not affect mortality or cardiovascular outcomes, but is associated with fewer exacerbations of COPD and is well tolerated. Fluticasone furoate, alone or in combination with vilanterol, appears to reduce the rate of decline in FEV_1.

Members of the Steering Committee

Jørgen Vestbo (co-chair, UK), Robert Brook (USA), Peter Calverley (UK), Bartolome Celli (USA), Fernando Martinez (USA), David Newby (UK), Courtney Crim, (co-chair, GlaxoSmithKline, USA), Julie Anderson (GlaxoSmithKline, UK), Julie Yates (GlaxoSmithKline, USA).

Members of the Independent Data Monitoring Committee

Peter Lange (chair, Denmark), Richard Kay (UK), Mark Dransfield (USA), Sanjay Rajagopalan (USA).

Members of the Clinical Endpoint Committee

Robert Wise (chair, USA), Dennis Niewoehner (USA), Camilo Gomez (USA), Sheldon Madger (Canada), Martin Denvir (UK), Pierre Amarenco (France).

Declaration of interests

Dr. Vestbo reports personal fees from GlaxoSmithKline during the conduct of the study as well as personal fees from GlaxoSmithKline, Chiesi Pharmaceuticals, Boehringer-Ingelheim, Novartis, and AstraZeneca outside the submitted work. Ms. Anderson is an employee of GlaxoSmithKline and therefore reports personal fees from GlaxoSmithKline during the conduct of the study as well as outside the submitted work. Dr. Brook reports personal fees from GSK during the conduct of the study. Dr Calverley reports personal fees from GlaxoSmithKline during the conduct of the study as well as personal fees from Boehringer-Ingelheim, GSK, AstraZeneca and Takeda outside the submitted work. Dr Celli reports personal fees from GlaxoSmithKline during the conduct of the study as well as personal fees from Boehringer-Ingelheim, AstraZeneca, Almirall, Rox Medical, and Novartis outside the submitted work. Dr Crim is an employee of GlaxoSmithKline and therefore reports personal fees from GlaxoSmithKline during the conduct of the study as well as outside the submitted work. Dr. Martinez reports non-financial support from GlaxoSmithKline during the conduct of the study as well as personal fees from Forest, Janssens, Nycomed/Takeda, Actelion, Amgen, Astra Zeneca, Carden Jennings, CSA Medical, Ikaria, Genentech, Merck, Pearl, Pfizer, Roche, American College of Chest Physicians, CME Incite, Center for Healthcare Education, Inova Health System, MedScape, Miller Medical, National Association for Continuing Education, Paradigm, Peer Voice, Projects in Knowledge, St. John's Hospital, St. Mary's Hospital, University of Illinois Chicago, University of Virginia, UpToDate, Wayne State University, Boehringer Ingelheim, Bayer, Merion, Informa, GlaxoSmithKline, Western Society of Allergy and Clinical Immunology, Theravance, Novartis, Haymarket, Annenberg, Academic CME, Integritas, Unity, and Sunovion outside the submitted work. Ms. Yates is an employee of GlaxoSmithKline and therefore reports personal fees from GlaxoSmithKline during the conduct of the study as well as outside the submitted work. Dr. Newby reports personal fees from GSK during the conduct of the study.

Contribution to manuscript:

JV and DN wrote the draft manuscript. All authors discussed the draft and provided comments and suggestions for change. All authors have approved the final manuscript. No medical writer was involved.

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Table 1

Baseline characteristics of study participants

		Placebo n=4,111	Fluticasone furoate n=4,135	Vilanterol n=4,118	Combination therapy n=4,121
Age (year)		65±8	65±8	65±8	65±8
Female Sex		1040 (25%)	1082 (26%)	1065 (26%)	1009 (24%)
Race	**White**	3328 (81%)	3358 (81%)	3339 (81%)	3332 (81%)
	Asian	682 (17%)	683 (17%)	680 (17%)	679 (16%)
	Other	101 (2%)	94 (2%)	99 (2%)	110 (3%)
BMI (kg/m^2)		28±6	28±6	28±6	28±6
Current Smokers		1936 (47%)	1945 (47%)	1929 (47%)	1868 (45%)
Smoking History (pack-years)		41±25	41±24	41±24	41±24
Post-bronchodilator FEV_1 (L)		1·70±0·40	1·70±0·41	1·70±0·40	1·70±0·40
Predicted post-bronchodilator FEV_1 (%)		59·7±6·1	59·6±6·1	59·7±6·1	59·7±6·1
FEV_1 reversibility (%) (as a percentage of pre-bronchodilator FEV_1)		8·4±12·1	7·9±11·7	8·3±12·2	8·0±11·8
Pre-study COPD therapy					
Long-acting beta-agonist		1417 (34%)	1432 (35%)	1464 (36%)	1456 (35%)
Long-acting muscarinic-agonist		659 (16%)	619 (15%)	634 (15%)	638 (15%)

		Placebo n=4,111	Fluticasone furoate n=4,135	Vilanterol n=4,118	Combination therapy n=4,121
Inhaled corticosteroid		1349 (33%)	1369 (33%)	1374 (33%)	1394 (34%)
Pre-study exacerbations in 12 month prior to study	0	2447 (60%)	2546 (62%)	2500 (61%)	2528 (61%)
	1	1044 (25%)	990 (24%)	988 (24%)	998 (24%)
	2+	620 (15%)	599 (14%)	630 (15%)	595 (14%)
Cardiovascular inclusion criteria[a]					
Manifest disease					
Coronary artery disease		2103 (51%)	2119 (51%)	2044 (50%)	2113 (51%)
Peripheral arterial disease		766 (19%)	755 (18%)	817 (20%)	807 (20%)
Previous stroke		404 (10%)	418 (10%)	387 (9%)	386 (9%)
Previous myocardial infarction		658 (16%)	664 (16%)	722 (18%)	730 (18%)
Diabetes with target organ disease		374 (9%)	355 (9%)	377 (9%)	397 (10%)
At risk					
Hypercholesterolaemia		2112 (66%)	2051 (65%)	2191 (67%)	2125 (66%)
Hypertension		2861 (89%)	2835 (89%)	2900 (89%)	2882 (90%)
Diabetes mellitus		850 (27%)	870 (27%)	874 (27%)	886 (28%)
Peripheral arterial disease		279 (9%)	264 (8%)	301 (9%)	310 (10%)
Baseline Cardiovascular Therapy					
Any medication		3996 (97%)	4009 (97%)	3996 (97%)	4021 (98%)
Anti-thrombotic medication		2292 (56%)	2316 (56%)	2295 (56%)	2384 (58%)
Lipid Lowering medication		2751 (67%)	2746 (66%)	2797 (68%)	2829 (69%)

	Placebo n=4,111	Fluticasone furoate n=4,135	Vilanterol n=4,118	Combination therapy n=4,121
Renin-angiotensin aldosterone inhibitor therapy	2887 (70%)	2841 (69%)	2862 (69%)	2932 (71%)
Beta-blockers	1389 (34%)	1458 (35%)	1376 (33%)	1444 (35%)
Calcium Channel Blockers	1551 (38%)	1606 (39%)	1569 (38%)	1593 (39%)
Nitrates	613 (15%)	556 (13%)	569 (14%)	556 (13%)
Diuretics	1508 (37%)	1541 (37%)	1549 (38%)	1550 (38%)

a. Patients can have multiple cardiovascular diseases or risks at study entry

Mean±standard deviation, n (%)

FEV_1, forced expiratory volume in one second; COPD, chronic obstructive pulmonary disease

Table 2

Reported adverse events among 16,568 patients in the safety population

	Placebo n=4,131	**Fluticasone furoate n=4,157**	**Vilanterol n=4,140**	**Combination therapy n=4,140**
Any adverse event	2782 (67%)	2820 (68%)	2809 (68%)	2780 (67%)
Adverse event leading to discontinuation of study medication	397 (10%)	367 (9%)	370 (9%)	342 (8%)
Serious adverse event	918 (22%)	929 (22%)	972 (23%)	961 (23%)
Fatal adverse event	192 (5%)	183 (4%)	198 (5%)	182 (4%)
Total exposure to study medication (patient-years)	6614	6889	6955	7038
Adverse events of special interest: Number of patients (%) and [rate per 100 patient-years]*				
Local steroid events	146 (4) [2·7]	209 (5) [3·9]	152 (4) [2·5]	225 (5) [4·2]
All cardiovascular events	695 (17) [16·4]	699 (17) [15·7]	707 (17) [15·7]	735 (18) [16·3]
Cardiac arrhythmias	211 (5) [4·1]	229 (6) [4·1]	224 (5) [3·9]	209 (5) [3·9]
Lower Respiratory Tract	226 (5)	238 (6)	220 (5)	221 (5)

Infections excluding pneumonia	[4·7]	[4·5]	[4·2]	[4·2]
Pneumonia	214 (5) [3·8]	228 (5) [4·2]	163 (4) [2·8]	237 (6) [3·9]
Hypersensitivity	143 (3) [2·6]	147 (4) [2·7]	160 (4) [2·8]	175 (4) [3·0]
Bone disorders including fractures	78 (2) [1·3]	79 (2) [1·5]	88 (2) [1·6]	96 (2) [1·6]
Hyperglycaemia/new onset diabetes mellitus	156 (4) [2·7]	153 (4) [2·6]	134 (3) [2·3]	148 (4) [2·3]
Corticosteroid-associated eye disorder	43 (1) [0·8]	62 (1) [1·0]	59 (1) [1·0]	57 (1) [1·0]
Hyper- or hypokalaemia	23 (<1) [0·3]	23 (<1) [0·3]	28 (<1) [0·4]	31 (<1) [0·5]
Tremor	11 (<1) [0·2]	11 (<1) [0·2]	16 (<1) [0·2]	12 (<1) [0·2]
Adrenal Suppression	1 (<1) [<0·1]	3 (<1) [<0·1]	0	1 (<1) [<0·1]

* Defined as adverse events of interest associated with the known pharmacological action of ICS or LABA therapy

Table 3

Primary and secondary outcomes and exacerbations of chronic obstructive pulmonary disease

	Placebo **n=4,111**	**Fluticasone furoate** **n=4,135**	**Vilanterol** **n=4,118**	**Combination therapy** **n=4,121**
All-cause mortality P value vs placebo	275 (6·7%)	251 (6·1%) P = 0·284	265 (6·4%) P = 0·655	246 (6·0%) P = 0·137
Cause-specific mortality				
Cardiovascular	122	97	118	108
Pulmonary	35	34	33	35
Cancer	62	59	61	56
Other	20	21	25	22
Unknown	36	40	28	25
Decline in post-bronchodilator FEV_1 (mL per year) Nominal p-value vs placebo*	46±2·5	38±2·4 P = 0·026	47±2·4 P = 0·654	38±2·4 P = 0·019
First Composite Cardiovascular Event Nominal p-value vs placebo*	173 (4·2%)	161 (3·9%) P = 0·317	180 (4·4%) P = 0·908	174 (4·2%) P = 0·478
Myocardial Infarction	38	45	44	46

	Placebo n=4,111	Fluticasone furoate n=4,135	Vilanterol n=4,118	Combination therapy n=4,121
Unstable Angina	26	16	22	19
Stroke	33	33	30	31
Transient Ischemic Attack	8	7	12	7
Sudden Death	62	53	62	63
Procedural Death	1	1	0	0
Other Cardiovascular Death	5	6	10	8
Annual Rate of Moderate and Severe Exacerbations	0·35	0·31	0·31	0·25
Annual Rate of Severe Exacerbations	0·07	0·06	0·06	0·05

n (%), mean± standard error

FEV_1: forced expiratory volume in 1 second;

* All p-values are versus placebo and are nominal for descriptive purposes only

Figure legends:

Figure 1

Consort diagram describing patient flow through the study.

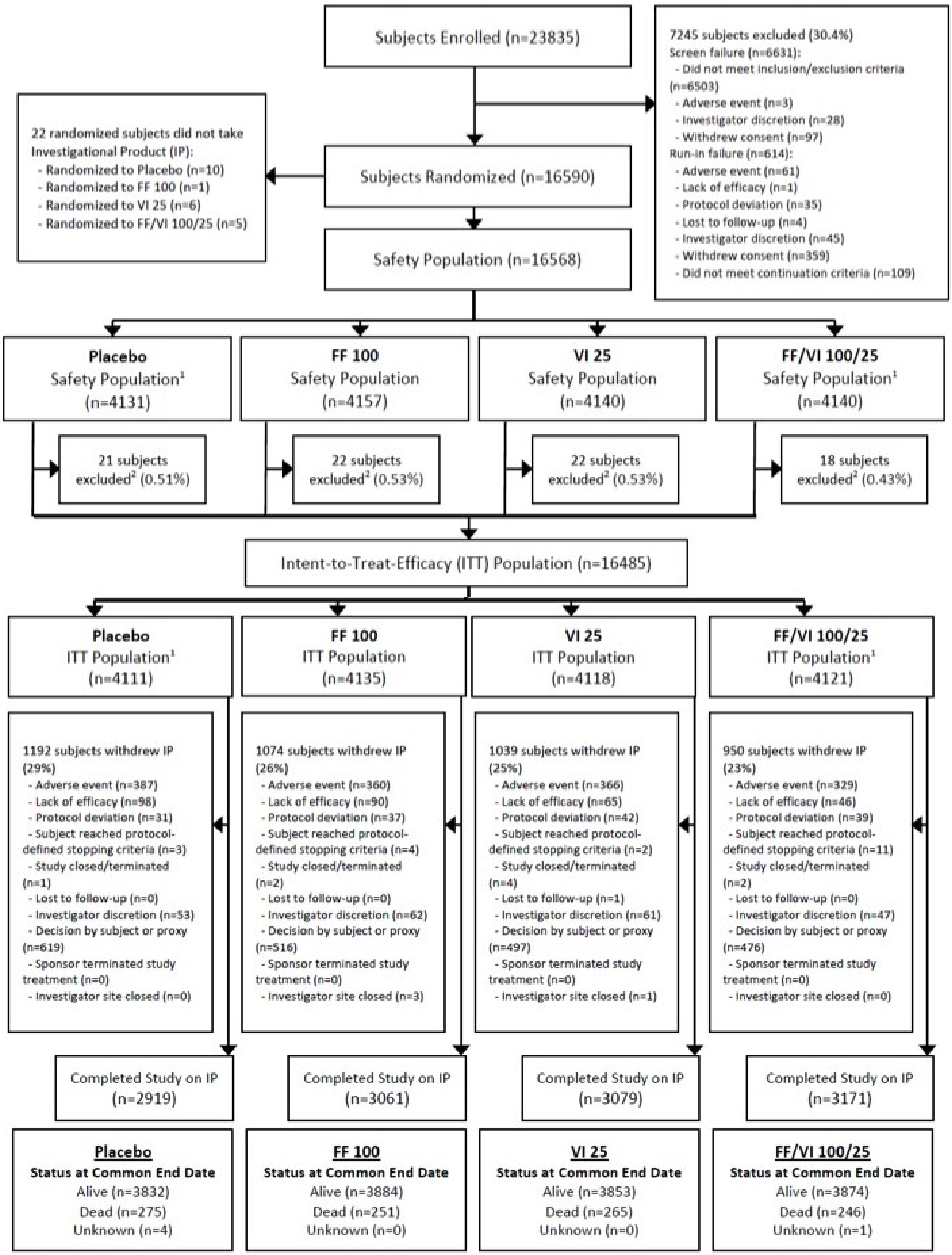
Figure 2

Probability of death (primary endpoint) in patients receiving placebo (black), fluticasone furoate (orange; FF), vilanterol (green; VI) and combined fluticasone furoate and vilanterol (blue; FF/VI) therapy.

Figure 3

On-treatment rate of decline in forced expiratory volume in one second (FEV_1) (B; secondary endpoint) in patients receiving placebo (black), fluticasone furoate (orange; FF), vilanterol (green; VI) and combined fluticasone furoate and vilanterol (blue; FF/VI) therapy. Error bars represent 95% CIs.

Figure 1



[1] 1 subject randomised to Placebo in ITT population is assigned to FF/VI, the treatment the subject received for the majority of the study, in the safety population.
[2] Excluded subjects were recruited at sites that were closed due to the result of audit findings or other information implying that the integrity of the data had been compromised.

Figure 2

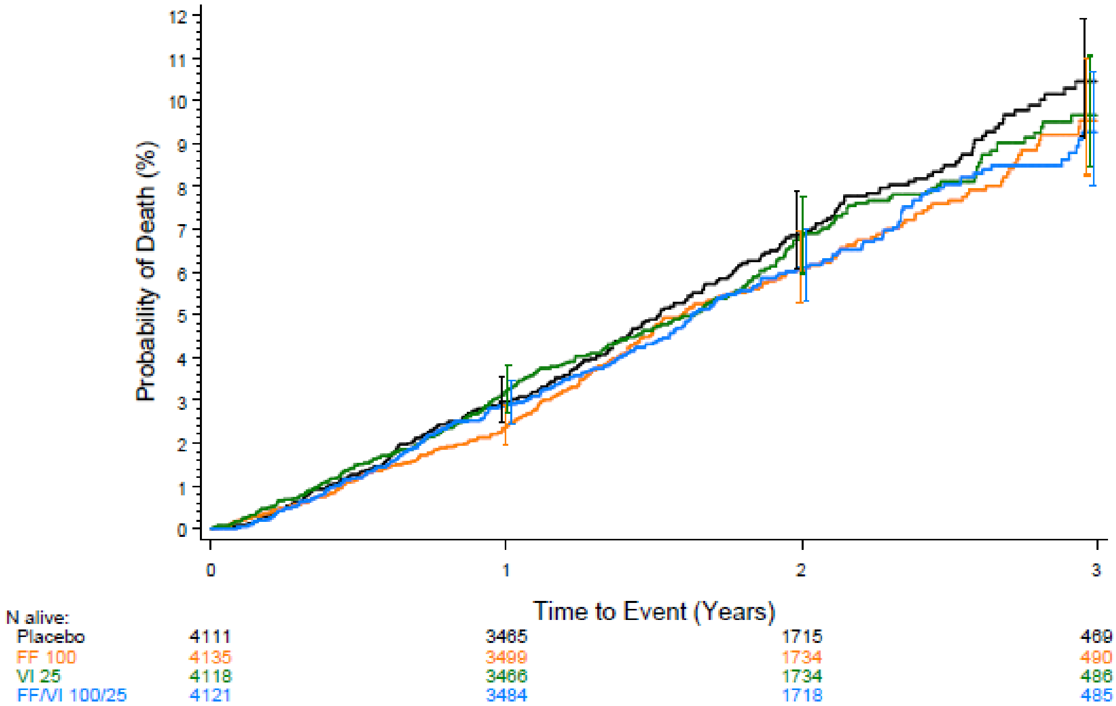


Figure 3